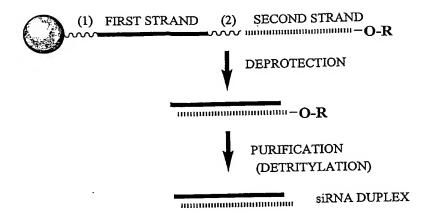
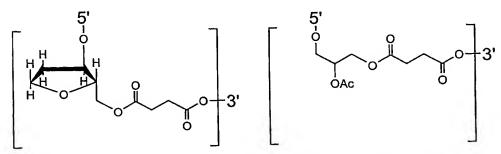
## Figure 1



= SOLID SUPPORT

R = TERMINAL PROTECTING GROUP FOR EXAMPLE: DIMETHOXYTRITYL (DMT)

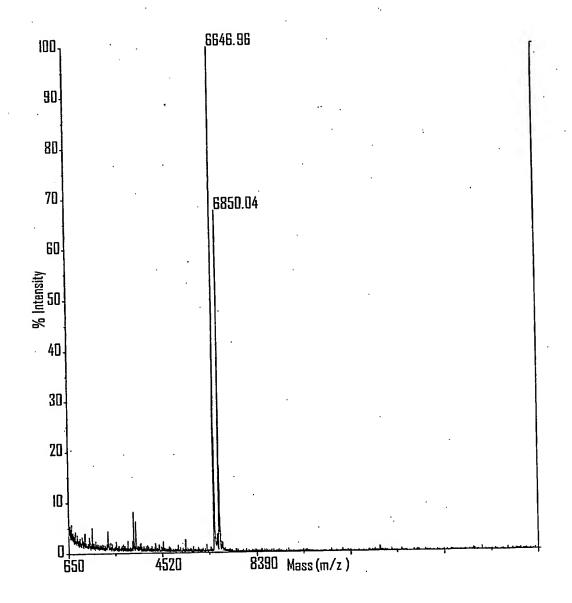
(1) = CLEAVABLE LINKER
(FOR EXAMPLE: NUCLEOTIDE SUCCINATE OR
(2) INVERTED DEOXYABASIC SUCCINATE)

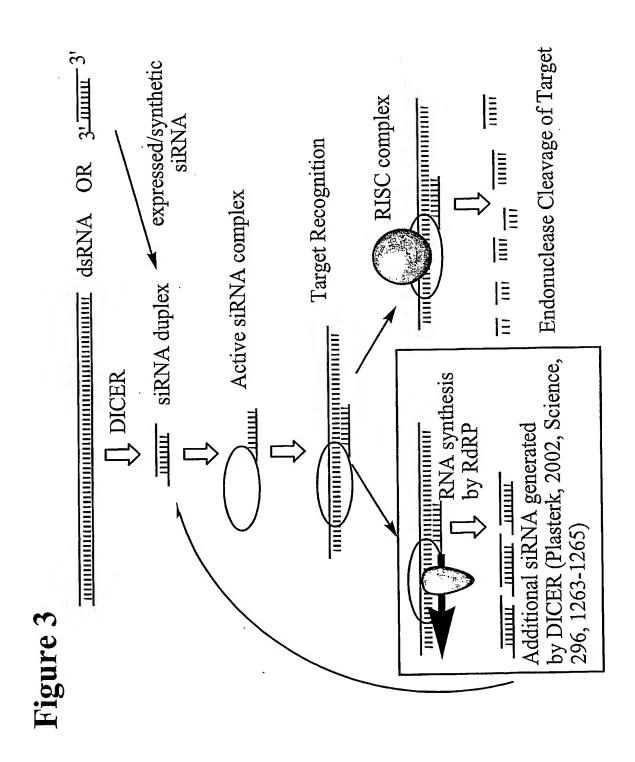


INVERTED DEOXYABASIC SUCCINATE LINKAGE

GLYCERYL SUCCINATE LINKAGE

Figure 2

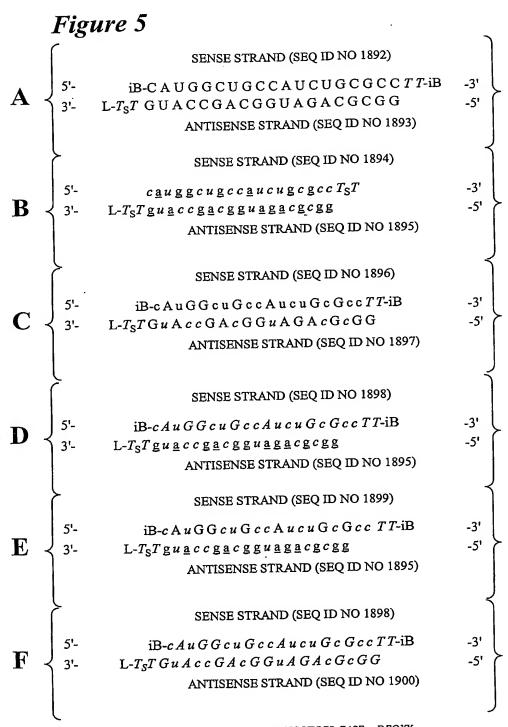




	F	igu	re 4	_
			SENSE STRAND (SEQ ID NO 1883) ALL POSITIONS RIBONUCLEOTIDE EXCEPT POSITIONS (N N)	
A		5'-	В-ИИИИИИИИИИИИИИИИИИИИИ	-3'
	•	3'-	L-(N <sub>s</sub> N) NNNNNNNNNNNNNNNNNN	-5'
			ANTISENSE STRAND (SEQ ID NO 1884) ALL POSITIONS RIBONUCLEOTIDE EXCEPT POSITIONS (N N)	
В	SENSE STRAND (SEQ ID NO 1885) ALL PYRIMIDINES = 2'-FLUORO AND ALL PURINES = 2'-OM EXCEPT POSITIONS (			
		5'-	$(N_sN)$ $N$	-3'
	-	3'-	$ extsf{L-(N_sN)}$ $ extsf{N}$	-5'
		ALL	ANTISENSE STRAND (SEQ ID NO 1886) PYRIMIDINES = 2'-FLUORO AND ALL PURINES = 2'-O-ME EXCEPT POSITIONS (	ии
		<u></u>		)
C			SENSE STRAND (SEQ ID NO 1887) ALL PYRIMIDINES = 2'-O-ME OR 2'-FLUORO EXCEPT POSITIONS (N N)	
		5'-	В-И И И И И И И И И И И И И И И И И И И	-3'
	4	3'-	L-(N <sub>s</sub> N) N N N N N N N N N N N N N N N N N N	-5'
			ANTISENSE STRAND (SEQ ID NO 1888) ALL PYRIMIDINES = 2'-FLUORO EXCEPT POSITIONS (N N)	
		$\mathcal{C}$	SENSE STRAND (SEO ID NO 1889)	)
D		ALL P	SENSE STRAND (SEQ ID NO 1889) YRIMIDINES = 2'-FLUORO EXCEPT POSITIONS (N N) AND ALL PURINES = 2'-DE	
		5'-	В-ИИИИИИИИИИИИИИИИИИИИИ	-3'
	~	3'-	L-(N <sub>s</sub> N) NNNNNNNNNNNNNNNNNN	-5' {
		ALL	ANTISENSE STRAND (SEQ ID NO 1886) PYRIMIDINES = 2'-FLUORO AND ALL PURINES = 2'-O-ME EXCEPT POSITIONS (	(מ מ
E		ر آ	SENSE STRAND (SEQ ID NO 1890) ALL PYRIMIDINES = 2-FLUORO EXCEPT POSITIONS (N N)	
		5'-	В-N N N N N N N N N N N N N N N N N N N	-3'
	4	3'-	L-(NN) NNNNNNNNNNNNNNNNNN	-5' }
		ALL	ANTISENSE STRAND (SEQ ID NO 1886) PYRIMIDINES = 2'-FLUORO AND ALL PURINES = 2'-O-ME EXCEPT POSITIONS (	(מא
				)
F		ALL P	SENSE STRAND (SEQ ID NO 1889) YRIMIDINES = 2'-FLUORO EXCEPT POSITIONS (N N) AND ALL PURINES = 2'-DE	OXY
		5'-	В-ИИИИИИИИИИИИИИИИИИИИИИИИИИ	-3' [
	~	3'-	L-(N <sub>s</sub> N) N N N N N N N N N N N N N N N N N N	-5' (
		ALL P	ANTISENSE STRAND (SEQ ID NO 1891) YRIMIDINES = 2'-FLUORO EXCEPT POSITIONS (N N) AND ALL PURINES = 2'-DE	oxy
		POSIT	TIONS (NN) CAN COMPRISE ANY NUCLEOTIDE, SUCH AS DEOXYNUCI	LEOTIDES
		(eg. T) $B = A$	HYMIDINÉ) OR UNIVERSAL BASES BASIC, INVERTED ABASIC, INVERTED NUCLEOTIDE OR OTHER TERN HAT IS OPTIONALLY PRESENT	
		I = GI	LYCERYL OR B THAT IS OPTIONALLY PRESENT HOSPHOROTHIOATE OR PHOSPHORODITHIOATE THAT IS OPTIONALL	Y ABSENT

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lower case = 2'-O-Methyl or 2'-deoxy-2'-fluoro
italic lower case = 2'-deoxy-2'-fluoro
underline = 2'-O-methyl

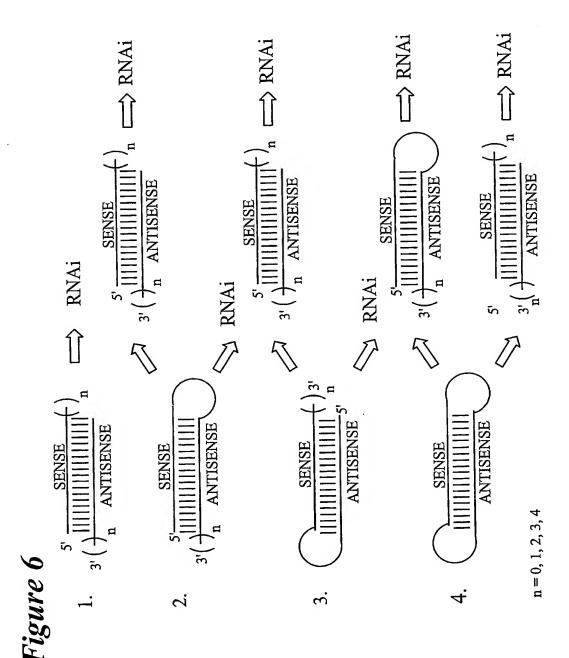
ITALIC UPPER CASE = DEOXY

IB = INVERTED DEOXYABASIC

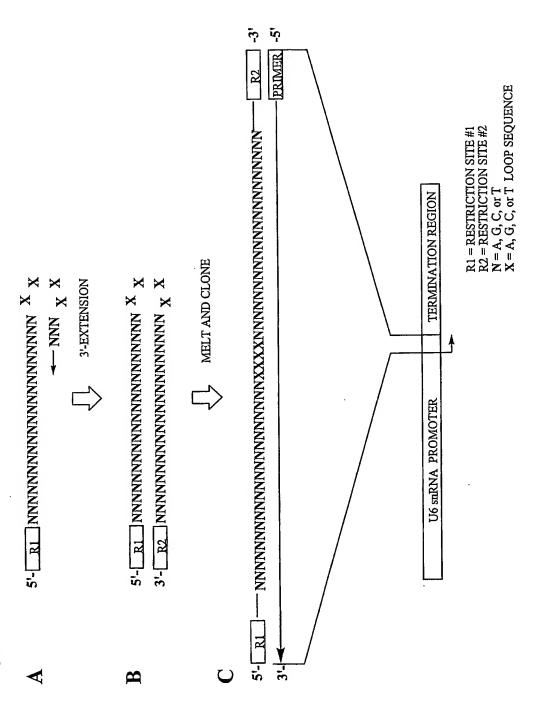
L = GLYCERYL MOIETY OR IB OPTIONALLY PRESENT

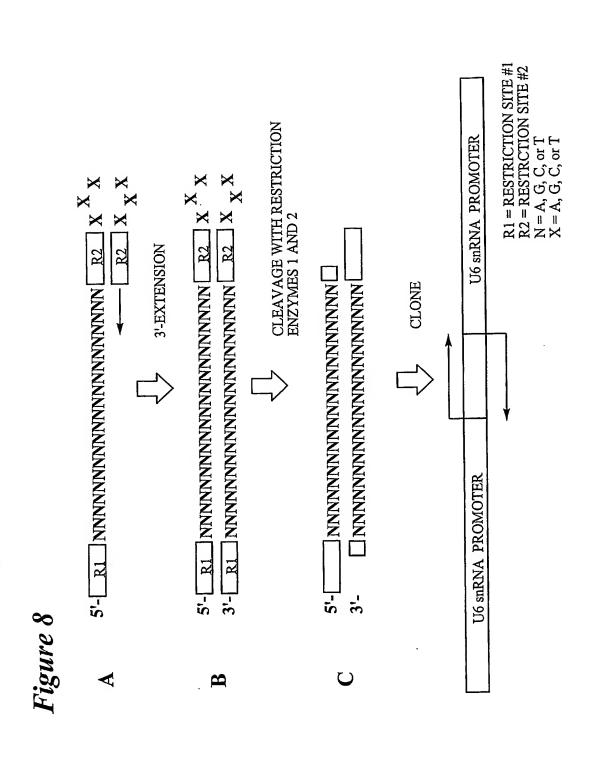
S = PHOSPHOROTHIOATE OR

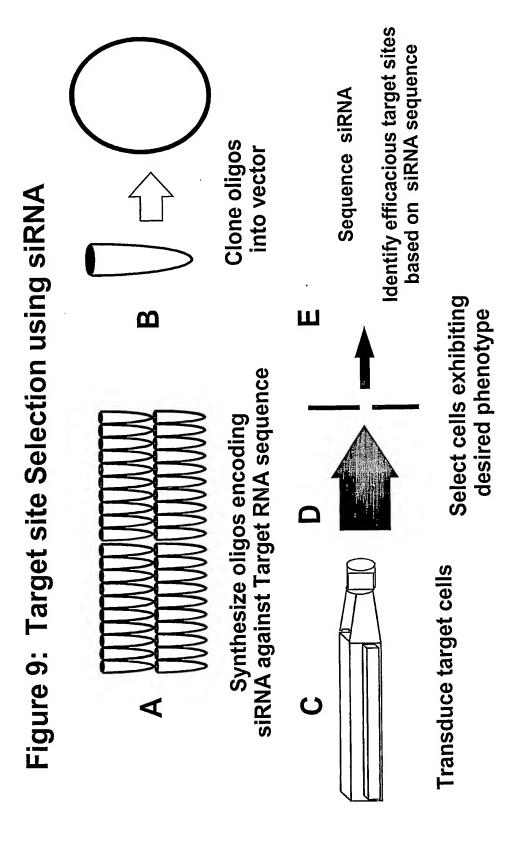
PHOSPHORODITHIOATE OPTIONALLY PRESENT





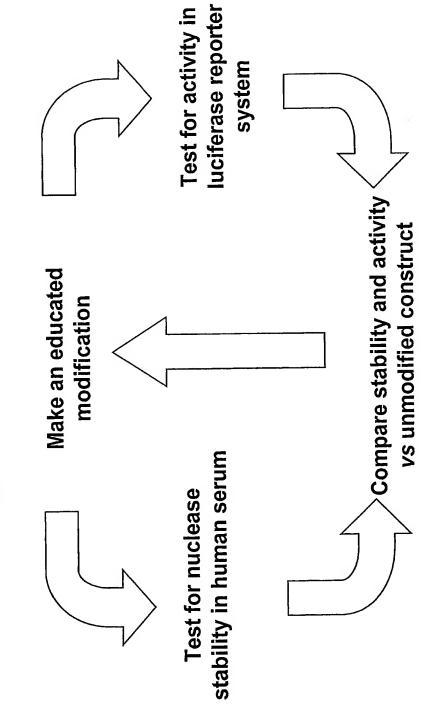






R = O, S, N, alkyl, substituted alkyl, O-alkyl, S-alkyl, alkaryl, or aralkyl B = Independently any nucleotide base, either naturally occurring or chemically modified, or optionally H (abasic).

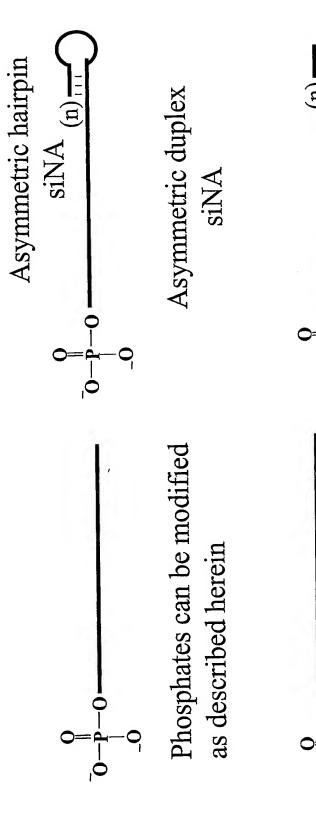
Figure 11: Modification Strategy



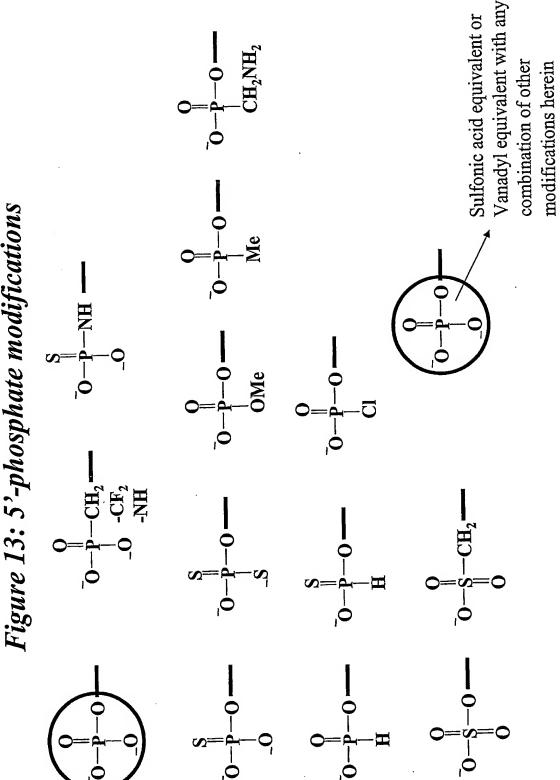
(n) = number of base

pairs (e.g. 3-18 bp)

## Figure 12: Phosphorylated siNA constructs



## Figure 13: 5'-phosphate modifications



strands to form duplex construct

<u>(</u>

Figure 14A: Duplex forming oligonucleotide constructs that utilize Palindrome or repeat sequences

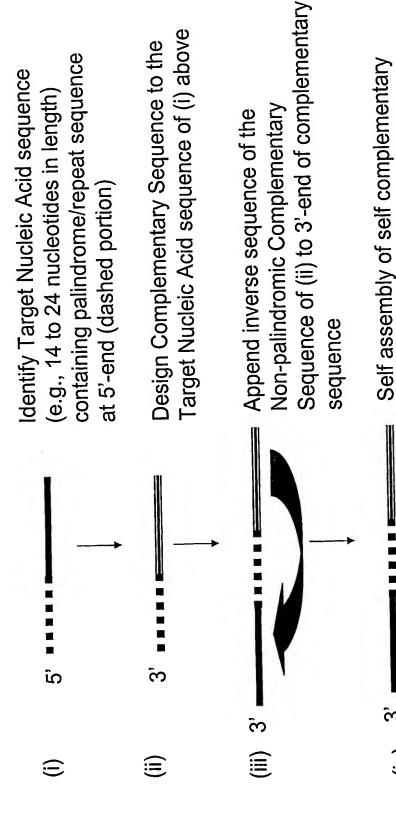


Figure 14B: Example of a duplex forming oligonucleotide sequence that utilizes a palindrome or repeat sequence

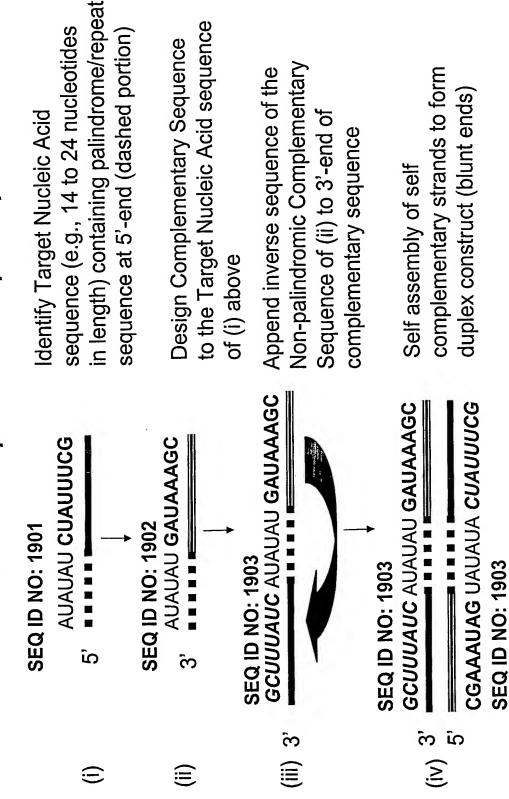


Figure 14C: Example of a duplex forming oligonucleotide sequence that utilizes a palindrome or repeat sequence, self assembly

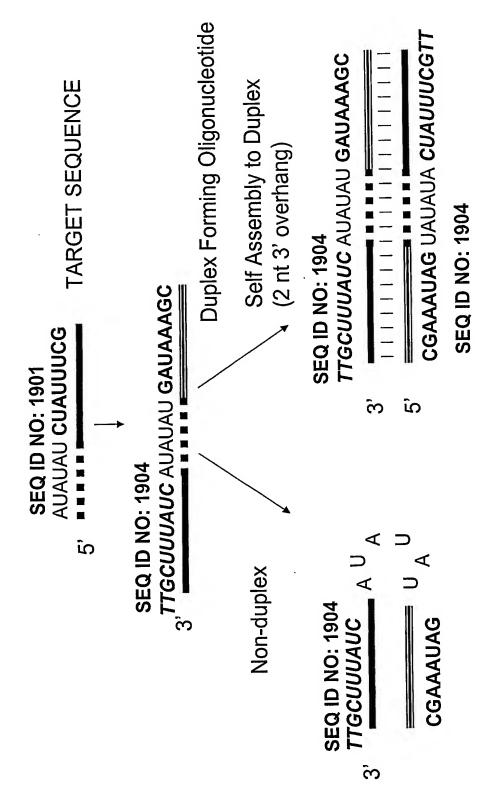


Figure 14D: Example of a duplex forming oligonucleotide sequence that utilizes a palindrome or repeat sequence, self assembly and inhibition

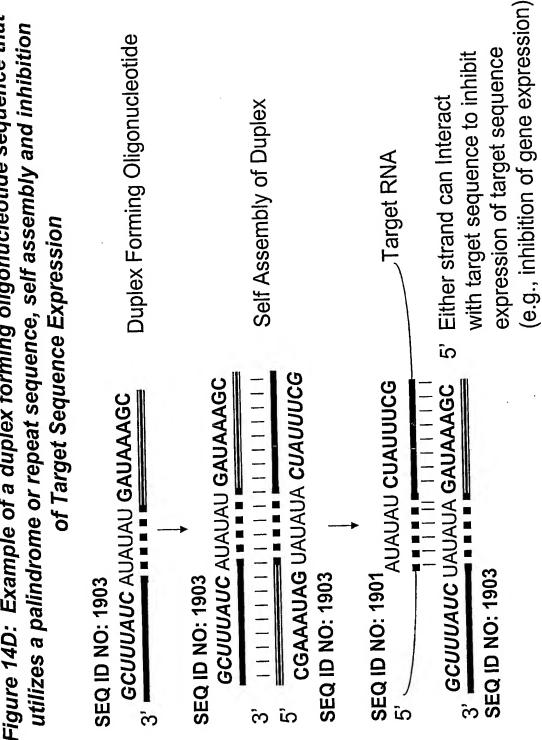
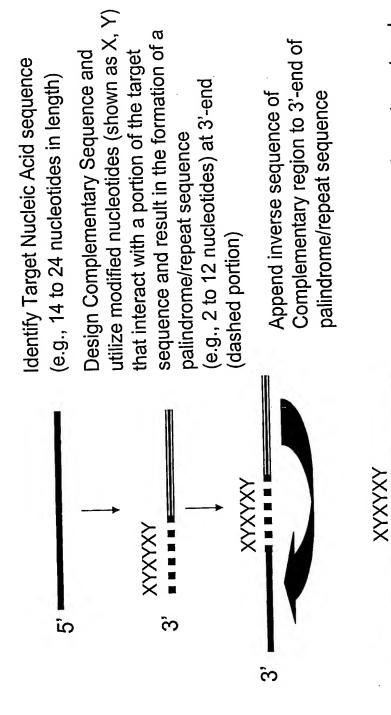


Figure 15: Duplex forming oligonucleotide constructs that utilize artificial palindrome or repeat sequences



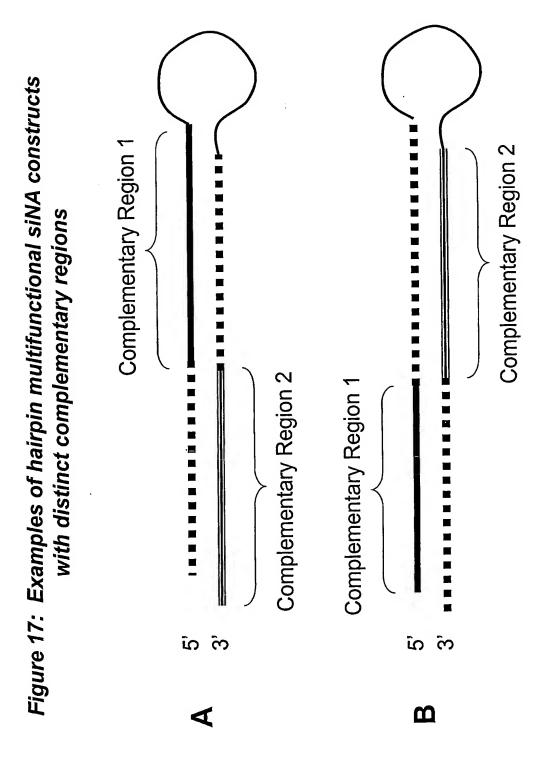
Hybridize self complementary strands to form duplex siNA construct

YXYXX

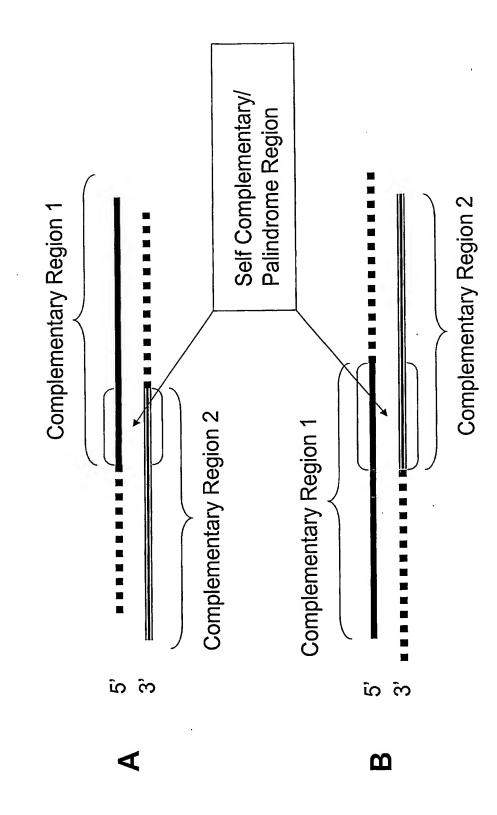
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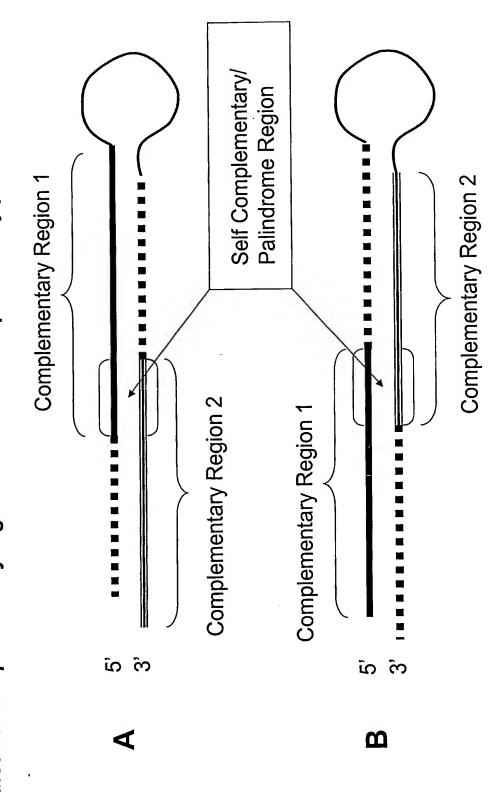
Figure 16: Examples of double stranded multifunctional siNA constructs with distinct complementary regions Complementary Region 2 Complementary Region 1 Complementary Region 2 Complementary Region 1 က် က်  $\hat{\Omega}$ ŝ  $\mathbf{\omega}$ 



distinct complementary regions and a self complementary/palindrome region Figure 18: Examples of double stranded multifunctional siNA constructs with



distinct complementary regions and a self complementary/palindrome region Figure 19: Examples of hairpin multifunctional siNA constructs with



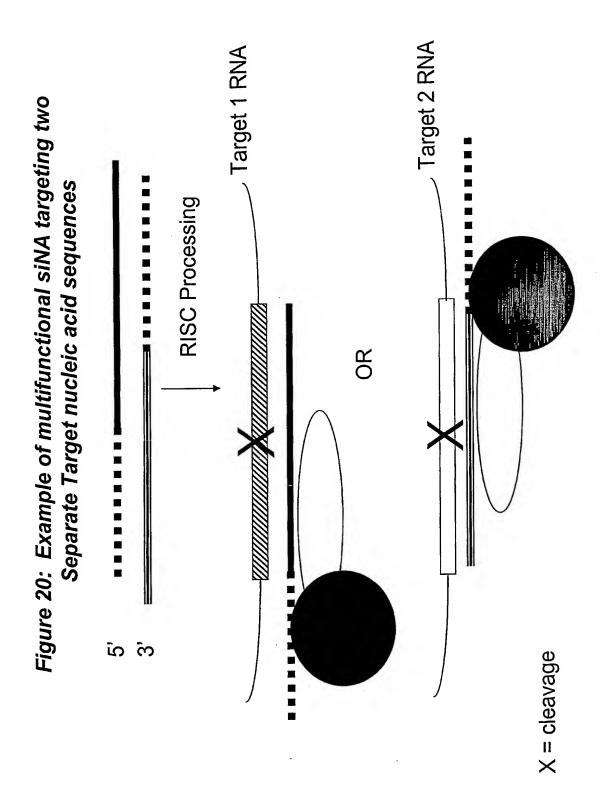


Figure 21: Example of multifunctional siNA targeting two regions within the same target nucleic acid sequence

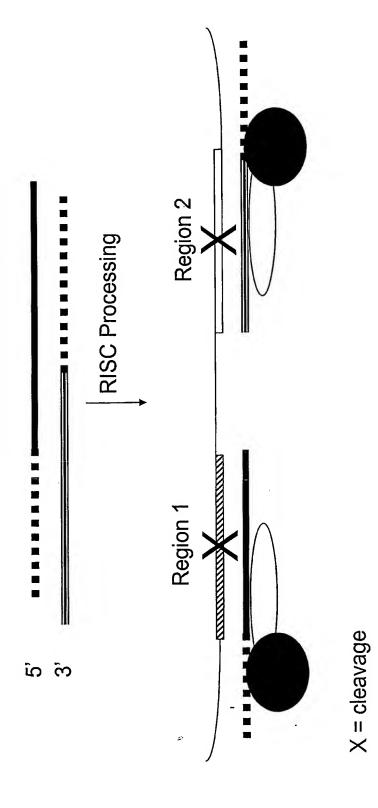
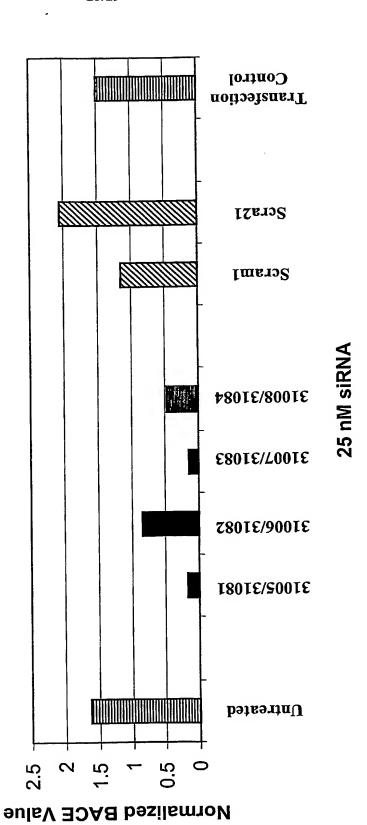


Figure 22: A549 24h BACE mRNA Expression



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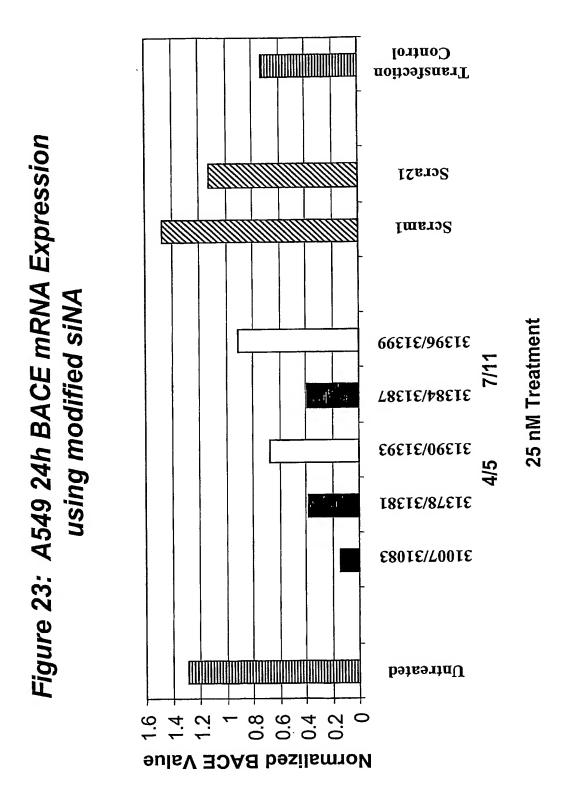


FIGURE 24

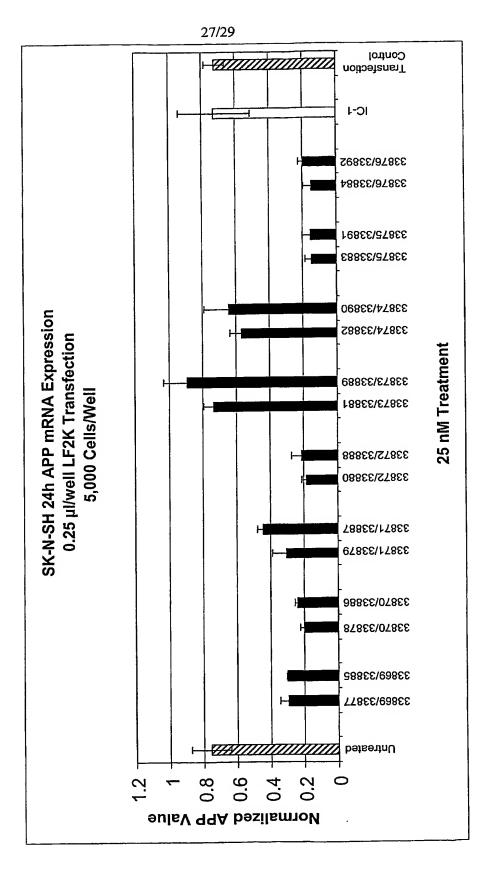
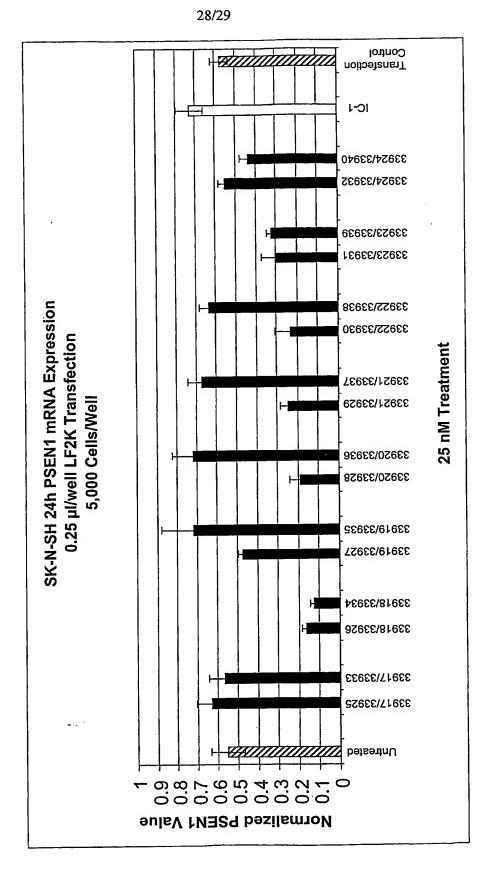


FIGURE 25



## FIGURE 26

